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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/870,937	05/30/2001	Bin Wu	PP-01623.002	8716

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EXAMINER	
LAMBERTSON, DAVID A	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 04/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/870,937	WU ET AL.	
	Examiner	Art Unit	
	David A. Lambertson	1636	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 24 March 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.

b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☒ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *1,3-5,21 and 23-26*.

   Claim(s) withdrawn from consideration: *6-19*.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☒ Other: *See Continuation Sheet*

Continuation of 5. does NOT place the application in condition for allowance because: Although Applicant's arguments have been addressed in the FINAL Office Action, they will be clarified on the record with regars to the statements made by Applicant in the presently submitted remarks. The response, which is substantial due to the length of Applicant's arguments, is contained on the attached sheets.

Continuation of 10. Other: The Information Disclosure Statement filed March 24, 2004 has been placed in the file, but it has not been considered on the record. Applicant has not complied with 37 CFR § 1.97 concerning the appropriate time for filing an IDS, specifically 37 CFR § 1.97(d).

It is additionally noted that the application still contains claims 6-19, which have been withdrawn from consideration. These claims mus be cancelled prior to any Notice of Allowance..

JAMES KETTER
PRIMARY EXAMINER

ADVISORY ACTION

Election/Restrictions

It is again reiterated that the election of SEQ ID NO: 1 is *not an election of species*. This was clearly set forth, not only in the Election/Restriction, but also in the First Office Action, page 2, in response to Applicant's election and traversal.

Response to Arguments

Applicant's arguments filed March 24, 2004 have been fully considered but they are not persuasive. Applicant provides the following grounds of traversal regarding the rejection under Written Description:

1. Applicant purports that the current situation (meaning antisense technology) is not a situation where Applicant must provide missing information; on the contrary, Applicant asserts the specification clearly provides all of the *possible* (emphasis added) antisense oligonucleotides claimed in the instant application by disclosing the KIAA0175 sequence (See Applicants remarks, page 6, second full paragraph).

2. Applicant argues that the Branch reference, provided in support of the Written Description rejection, actually supports Applicant's position. Applicant asserts that Branch supports the position that "written description in the antisense field is not an appropriate field to have to overcome because one of skill in the art would not expect a patentee to have provided 'on paper' a suitable antisense molecule," citing page 49 of Branch in support of their statement (see Applicant's Remarks, pages 6-7, the bridging paragraph).

3. Applicant argues that it would not be outside the scope of experimentation to determine which of the *possible* (emphasis added) antisense oligonucleotides are actually antisense molecules in that they have the functionality of an antisense molecule (i.e., capacity to inhibit the expression of its target nucleic acid)(See page 7, first full paragraph of Applicant's Remarks).

4. Applicant argues that the report by Monia *et al.* (*Nature Medicine* **2**: 668-675, 1996) more accurately reflects the state of the art, and provides an "excellent example of the successful use of [C-*raf*-1 kinase] antisense molecules *in vitro* and *in vivo*." Furthermore, Monia does not literally state that their experimentation is excessive or undue, and cites a second reference that purportedly successfully uses an antisense Cyclin D1 molecule (see for example pages 7-8, bridging and first and second full paragraphs of Applicant's Remarks).

Applicant's arguments have been considered, and are addressed as follows:

1. The key to Applicant's statements is that the antisense molecules are merely *possible* antisense molecules. The standard for satisfying the Written Description requirement (alternatively to the description of a representative number of members of the claimed genus, which is not present in the instant specification) is the disclosure of a *structure-function relationship* for the claimed genus that allows the skilled artisan *to envision* the claimed invention. Applicant clearly acknowledges that there is no such structure-function relationship set forth in the instant specification because the claimed antisense molecules are merely *possible* meaning that there is no description as to what structures will give the desired function. In support of the rejection, the Branch reference clearly indicates that there is much more to an antisense molecule than simple homology with the desired target. These arguments and sections

are clearly pointed out in the First and Final Office Actions. Thus, Applicant's own arguments that they have described all of the *possible* antisense molecules point out the deficiency in the Written Description.

2. On page 49, the paragraph bridging the middle and right columns of Branch, it is indicated that there is a great deal of thought that goes into designing (i.e., envisioning) an antisense molecule. Indeed, Branch establishes the difficulty in "envisioning a representative number of species" to satisfy a genus of antisense molecules for any given gene, thus supporting the argument of a lack of written description. The fact that it is difficult to design an antisense a molecule in no way absolves Applicant from satisfying the Written Description requirement in the instant application. Thus, Applicant's assertion that they should not be held to the standards set forth in 35 USC 112, first paragraph (in particular the Written Description standard), simply because it would be difficult to do, is unfounded and insufficient to overcome the instant rejection.

3. The scope of experimentation necessary to determine if a molecule is an antisense molecule is more appropriately an argument of enablement. The instant rejection is directed to the ability to "envision" an antisense molecule, and not the ability to make one. Therefore, Applicant's argument is moot, although the principles will be discussed below in response to Applicant's traversal of the enablement rejection.

4. Applicant attempts to rely on art that pre-dates the Branch reference used to traverse the instant rejection. In this aspect, the Office takes the position that the Monia reference does not accurately reflect the state of the art, as a later reference (i.e., Branch) clearly sets forth the deficiencies involved in envisioning antisense molecules. Furthermore, Applicant's argument is

flawed because, as set forth in Monia, only a limited number of molecules (~35%) showed any functional activity, and only one showed a good response; this certainly questions the ability of the skilled artisan to successfully envision a functional antisense molecule from a large genus of *possible* antisense molecules (i.e., which 30% of the claimed antisense molecules actually have antisense activity is entirely unknown). Finally, it is noted that the recitation of the alleged successful uses of antisense molecules to C-*raf*-1 kinase and cyclin D1 is non-analogous in terms of the particular antisense molecules claimed in the instant case because each sequence is different, and will have different functional requirements for their respective antisense molecules. The fact that someone has found an antisense molecule to another gene does not aid the skilled artisan in envisioning a functional antisense molecule to KIAA0175 because there are different sequences and structural considerations to be made when designing the particular antisense molecules; this is also set forth in Branch, as stated previously on the record.

In conclusion, Applicant has not provided any evidence that the Written Description requirement has been satisfied. Rather, Applicant has clearly indicated that only *possible* antisense molecules have been disclosed; i.e., there is no disclosed structure-function relationship as it regards the claimed invention. Applicant then goes on to assert that it is unreasonable to hold the instant invention to the Written Description standard because one reference cited in support of the rejection (Branch) clearly indicates that there are a lot of variables and considerations to be made when designing (i.e., envisioning) an oligonucleotide. It is the fact that these variables and considerations exist, and are so difficult to circumvent that necessitates a written description rejection of the claimed genus of antisense molecules. It is inappropriate for Applicant to use the difficulty in providing a written description in the instant case as a shield

against meeting the Written Description requirement of 35 USC 112, first paragraph. As such, the rejection is maintained in view of Applicant's remarks.

Applicant's arguments filed March 24, 2004 have been fully considered but they are not persuasive. Applicant provides the following grounds of traversal with regard to the Enablement rejection:

1. With regard to the "Quantity of Experimentation," Applicant asserts that they have provided a routine assay that can be used to successfully identify any KIAA0175 antisense molecule to determine if a given oligonucleotide serves as an antisense molecule. Applicant asserts that this experimentation is not undue and unpredictable, and purports that the Office has provided no evidence to suggest that it is. Applicant then addresses the Branch reference, asserting that Branch does not establish antisense technology as requiring undue and unpredictable trial and error experimentation.

2. With regard to the "Amount of Direction or Guidance Provided," Applicant asserts that the nature of the invention is not necessarily gene therapy, suggesting that the claimed antisense oligonucleotides could be used for research purposes to study the relationship between *in vitro* and *in vivo* activity.

3. With regard to the "Presence of Working Examples," Applicant asserts that there are working examples presented on pages 39-40 of the instant specification indicating a method for using an antisense oligonucleotide, and this method would be applicable to all antisense oligonucleotides. Applicant then indicates that Branch uses the term "diamond mines" to describe antisense

technology, and suggests that the Office's characterization of the genre as purely problematic is inaccurate.

4. With regard to the "Nature of the Invention," Applicant indicates that the Office has inappropriately focused on gene therapy as the use for the claimed invention. Applicant asserts that the invention can be used to study the effects of inhibiting KIAA0175 expression on the sensitization of cells to DNA damaging agents. Applicant again asserts that the invention is much broader in scope than antisense gene therapy.

5. With regard to the "State of the Prior Art," Applicant asserts that the novelty of the invention is with regard to the identity of the sequence set forth as KIAA0175, and not to antisense technology or procedures in general. Applicant then asserts that the overall conclusion with regard to the invention is that it is not unpredictable because: (a) one expects to screen candidates for their ability to act as antisense molecules; (b) in a screen of 34 particular antisense molecules (notably, completely unrelated to the target molecule indicated in the instant specification), 3% were highly effective; and (c) non-antisense effects are not *per se* unwanted.

6. With regard to the "Relative Skill in the Art," Applicant states that "Applicant's did not specifically state that one of skill would be able to reasonably predict that any nucleic acid complimentary to KIAA0175 would serve as an antisense molecule...the cited references (Branch, Jen) establish that such prediction was not expected at the time of filing" (original emphasis).

7. With regard to the "Predictability or Unpredictability of the Art," Applicant asserts that the skilled artisan would be able to predict that an inhibitory effect of a possible antisense molecule would be detectable.

8. With regard to the "Breadth of the Claims," Applicant asserts that one of skill in the art could routinely identify or construct any nucleic acid meeting the limitations of the claims.

Applicant's arguments have been substantially addressed in the previous Office action. However, the Office offers the following additional comments to address the specific new comments raised by Applicant in the After Final response:

1. Applicant is reminded that the Enablement requirement is directed to the ability to "make and use" the invention, and not necessarily to the ability to "identify" the invention. In the instant case, it would require undue and unpredictable trial and error experimentation to *make* an antisense molecule for KIAA0175 because the skilled artisan would need to randomly test all complementary sequences for antisense activity to identify such a molecule prior to being able to make it. In direct contrast to Applicant's assertion, Branch does establish that this is undue and unpredictable. Branch specifically states "[B]ecause it is *very difficult to predict* what portions of an RNA molecule will be accessible *in vivo*, effective *antisense molecules must be found empirically* by screening large numbers of candidates for their ability to act inside cells" (page 49, left column, last paragraph; emphasis added); by definition, all empirical experimentation is undue and unpredictable. Thus, Branch does indicate that the invention requires undue and unpredictable experimentation. Furthermore, the ratio of 40% ineffective to 60% effective (incidentally, merely an unsubstantiated presumption by Applicant, as nowhere does it state that the remaining 60% of the molecules are effective) only relates to antisense molecules for a single gene, C-*raf*-1 kinase, which is totally unrelated in sequence to the target of the instant application. Therefore, not only is this ratio virtually irrelevant to the instant invention, but it

also shows that making a functional antisense molecule is equivalent to flipping a coin, as there is barely better than a 50% chance of randomly obtaining such a molecule.

2 and 4. The ability to further study the antisense molecule/target gene is not a real world use that can be used to meet the Enablement standard. It is impermissible to rely on further study of the invention (i.e., testing the relationship of *in vitro* and *in vivo* studies, or testing the effects of the antisense molecule on sensitivity of cells lacking the gene) as a credible, significant and substantial utility. Therefore, Applicant's assessment of the purported "broad scope of the invention" beyond gene therapy is inaccurate. Furthermore, while gene therapy is a substantial, significant and credible utility (thus obviating a utility rejection in the previous Office Actions), it is clearly not enabled as supported by the references cited in the previous Office Actions.

3. While applicant discloses sequences alleged as having antisense properties on pages 39-40, there is no demonstration of their use in gene therapy, which is highly unpredictable as set forth in the previous Office Actions. Therefore, these oligonucleotides have no enabled real world use, as it is well established that one must be able to use the claimed invention for an asserted real world activity in order to satisfy 35 USC § 112, first paragraph. Furthermore, these few alleged antisense molecules are in no way representative of the broad genus of antisense molecules claimed in the instant invention, there being no structure-function element that is conserved even amongst these few embodiments.

Applicant's reliance on the description of antisense technology as being a "diamond mine" neglects to also recognize that Branch describes them in the same sentence as being "quicksand." This comparison is driven by the unpredictability of antisense technology, which is the crux of the Enablement requirement. Thus, it is not that the Office is trying to indicate that

the field is entirely problematic, simply that one of skill in the art cannot predict the pitfalls or the successful embodiments of the claimed invention; this is especially true in light of the teachings of the instant specification, which provides no guidance as to which of the hundreds of thousands of *possible* antisense molecules are the "diamond mines" and which are "quicksand." Thus, the fact that antisense technology randomly provides "diamond mines" versus "quicksand" only serves to support the argument that the claimed invention is not enabled.

5 and 8. Applicant asserts that the nature of the invention is the identity of the gene that can be used for designing antisense molecules to it. It is again reiterated that the claims are directed to antisense molecules, and not the KIAA0175 sequence. Thus, this argument is moot. With regard to the overall conclusion that the invention does not demand an undue and unpredictable amount of trial and error experimentation, the issues which Applicant supplies have all been addressed above, save for the comments about non-antisense effects not being entirely unwanted, *per se*. In response to this comment, it is noted that the non-antisense effects are not at all contemplated by the instant specification, and are unpredictable as set forth in Branch. Therefore, such a statement does not support Applicant's claim that the invention does not require undue and unpredictable trial and error experimentation.

6. The statement, "Applicant's did not specifically state that one of skill would be able to reasonably predict that any nucleic acid complimentary to KIAA0175 would serve as an antisense molecule...the cited references (Branch, Jen) establish that such prediction was not expected at the time of filing" (original emphasis) completely summarizes the Enablement rejection. It is clear from this argument that the invention is unpredictable in both the specification and the state of the art. Applicant cannot use the unpredictable nature of the

invention to shield them from the enablement requirement; in other words, it is inappropriate for Applicant to argue that the prior art did not have a reasonable expectation of predicting antisense molecules, therefore it cannot be expected that Applicant meet such a standard. The fact that Branch and Jen indicate that antisense technology is unpredictable does not absolve Applicant from satisfying the enablement standard; indeed it is this unpredictability that *necessitates* the enablement rejection.

7. Applicant is arguing that Applicant can predict what a result will mean. The rejection does not question the ability of the skilled artisan to interpret a result; what is questioned is the ability "to make and use" an antisense molecule to necessarily give the desired result. As established above, Branch states, "[B]ecause it is *very difficult to predict* what portions of an RNA molecule will be accessible *in vivo*, effective *antisense molecules must be found empirically* by screening large numbers of candidates for their ability to act inside cells" (page 49, left column, last paragraph; emphasis added). This clearly establishes that the invention is unpredictable, in direct contrast to Applicant's argument that it is routine.

In conclusion, Applicant's assertion that the instant specification is enabled is unfounded and unsupported by evidence. Indeed, Applicant's own statements that "possible antisense molecules" have been described, and that they "did not specifically state that one of skill would be able to reasonably predict that any nucleic acid complimentary to KIAA0175 would serve as an antisense molecule...the cited references (Branch, Jen) establish that such prediction was not expected at the time of filing" support that the invention is not enabled. In contrast t Applicant's opinion-based statements, the Office has provided several references supporting the

unpredictable nature of both antisense technology and gene therapy using antisense molecules, which have not been disputed by any evidence. As such, the rejections are maintained for the reasons set forth in the First and Final Office Actions, with due consideration to the arguments made in the After Final amendment filed March 24, 2004.